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MEDICAL MANAGEMENT UPDATE *Editors: F. John Firriolo and Thomas Sollecito*

Dr. Donald Falace recently decided to retire from the position as editor of the Medical Management Update feature of the Journal. We were fortunate to have one of the world's pre-eminent authorities on the medical management of the dental patient overseeing this section.

As Editor in Chief, I thank him for his efforts for the Journal over the past several years and also for all the other contributions he has made to the dental profession through his writings and teaching. He is truly one of the stars of the dental universe.

James R. Hupp, Editor in Chief

Liver disease: Current perspectives on medical and dental management

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The liver has many essential functions, and liver disease presents a number of concerns for the delivery of medical and dental care. A number of conditions that cause liver dysfunction may be related to lifestyle and a variety of diseases. The purpose of this paper is to update dental providers regarding recent progress in liver disease research and to identify ways of caring effectively for patients with hepatic dysfunction. A Medline search from 1996-2003 was conducted using the following search terms: liver disease, hepatitis, autoimmune hepatitis, fulminant hepatitis, hemochromatosis, liver cirrhosis, and hepatic carcinoma. This update will focus on hepatitis, hemochromatosis, hepatic cirrhosis, hepatocellular carcinoma, and their characteristics pertinent to dental patient management.

HEPATITIS

Hepatitis has a number of potential causes, both infectious and non-infectious. Alcohol, prescription medications, and drug abuse are predominant non-infectious causes, while viruses and bacteria are important infectious etiologic factors. Viral and drug-induced hepatitis are examples of primary hepatitis. Secondary hepatitis may occur as a sequela of other disease entities such as mononucleosis, syphilis, and tuberculosis.[1]

Hepatitis A

Hepatitis A is caused by the Hepatitis A virus (HAV), an enterovirus of the Picornaviridae family. HAV is

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a single-stranded RNA virus surrounded by a protein capsid.[1] Transmission is primarily by the oral-fecal route. Various methods of spread are through contact of an infected person, traveling to an endemic region, and ingestion of contaminated food or water.[1]

Hepatitis A is typically a self-limiting disease and usually causes mild illness characterized by sudden onset of non-specific symptoms.[2] In children six years or younger, it is usually asymptomatic. In adults, infection may present with symptoms such as fever, fatigue, abdominal discomfort, diarrhea, nausea, and/or jaundice. Diagnosis is made based upon signs and symptoms in combination with serologic tests for IgM anti-HAV (positive with recent infection) and IgG anti-HAV (reflective of past infection and long-term immunity). The risk of acquiring HAV infection for health care workers (nosocomial transmission) is quite low.

One effective method of prevention of HAV infection is the administration of HAV immune globulin either before the exposure or within two weeks following exposure.[2] Immune globulin provides passive immunity toward HAV. There are currently two vaccines available that provide active immunization against HAV: Harvix® (Smith Kline Beecham) and Vaqta ® (Merck). Those considered to be at increased risk of HAV infection (people traveling internationally, drug users, people with chronic liver disease, and those with occupational risks) should be vaccinated.[2] Educating health care providers and the public about vaccine availability and efficacy can be effective in preventing HAV outbreaks.

Hepatitis B

Hepatitis B virus (HBV) is a DNA virus with a nuclear capsule enveloped by an outer lipid layer containing hepatitis B surface antigen (HBsAg). The nuclear capsule contains other viral components, including the hepatitis B core antigen (HBcAg), the e antigen (HBeAg), DNA, and DNA polymerase. HBV replicates within the hepatocyte through an intermediate step of reverse transcription mediated by viral polymerase.[3]

Sexual contact, intravenous drug use, and transfusion of blood and blood products are common modes of transmission. In Asia, HBV is commonly transmitted perinatally.[4] Transmission via saliva may be important to dentistry, as HbSAg is detectable in saliva of infected individuals.[5] Health care workers, particularly dentists, have three to five times the rate of HBV infection compared to the general population.[6]

Diagnosis of hepatitis B is made by assessing HBV DNA, HBsAg, and e antigen/antibody levels.[5] The symptoms of hepatitis due to HBV are similar to those of hepatitis A.[5] A younger individual who becomes infected with HBV has a higher risk for developing chronic HBV and hepatocellular carcinoma. Approximately 90% of adult HBV-infected patients experience a full recovery, but 5-10% of the patients will develop chronic hepatitis with complications such as cirrhosis and hepatocellular carcinoma.[7]

There are two vaccines available for HBV immunization that utilize recombinant DNA technology, Engerix-B® (Merck) and Recombivax® (Glaxosmith Kline). HBV vaccine is given in three doses over a six-month period and produces an effective antibody response in the majority of individuals. If a nonimmunized individual has a documented exposure to HBV, hepatitis B immune globulin can be provided and may offer postexposure protection.[2] Current guidelines call for HBV immunization as part of a childhood vaccination series.

The steps of HBV replication provide therapeutic targets for antiviral therapy. Nucleoside analogues interfere with viral DNA synthesis by blocking further synthesis when incorporated into viral DNA and/or competitively inhibiting viral polymerase.[3] Current protocols for treatment of HBV infection use interferon and nucleoside analogues such as lamivudine.[3] Other nucleosides with activity against hepatitis B currently being used are famciclovir and adefovir.[4]

Hepatitis C

Hepatitis C virus (HCV) is a blood-borne, single-stranded RNA flavivirus encoding for a capsid protein, two envelope proteins, and some nonstructural proteins.[1] People at increased risk include hemophiliacs, dialysis patients, and intravenous drug users, although transmission is now reduced due to blood and blood product screening. Other modes of transmission are sexual, perinatal, and idiopathic. Though the primary mode of transmission is through blood, HCV has also been detected in saliva. The main diagnostic test for HCV is the enzyme-linked immunosorbent assay (ELISA) for anti-HCV and RT-PCR; ELISA does not distinguish between exposure and infection, whereas RT-PCR can make this distinction.[8]

Eighty-five percent of patients with HCV will develop chronic hepatitis.[9] Chronic HCV infection is the major cause of cirrhosis and hepatocellular carcinoma. Acute HCV infection usually presents with mild flu-like symptoms, while chronic disease is variable in presentation. Patients may experience nonspecific symptoms such as fatigue, nausea, and/or abdominal pain.[5] Chronic HCV infection is normally a slow, progressive disease that may produce few or no symptoms for many years after infection. Some patients develop chronic infection and suffer no significant liver damage, while others progress quickly to liver cirrhosis and may develop hepatocellular carcinoma.[10] Factors that may impact progression include age, gender, chronic alcohol abuse, and quantity of virus at exposure. Disease appears to be more aggressive in patients that acquire HCV after age 40 and may be more progressive in men than women.[10] HCV patients who abuse alcohol are more likely to develop cirrhosis than those who do not.[10]

Current management includes combination therapy with interferon and ribavirin.[11] Common side effects are nausea, fatigue, and malaise. Severe side effects of combination therapy are hemolytic anemia, leukocytopenia, and thrombocytopenia. Ribavirin has been associated with teratogenic effects and must be used cautiously.[8] Patients who relapse or who do not respond to interferon therapy may respond to combination or high-dose therapy.[8] A liver transplant is considered for patients with end-stage liver disease due to chronic hepatitis C.

Future treatment of hepatitis C may include agents that specifically target the virus rather than current nonspecific forms of antiviral therapy.[12] Research is focused on targeting the helicase and polymerase crucial to HCV replication. Other therapeutic targets are the viral proteases and the 5′ and 3′ strands of HCV RNA. Anti-sense RNAs, ribozymes, RNA decoys, and DNA oligonucleotides with the ability to prevent HCV replication are being studied.[8]

Hepatitis D

Hepatitis D virus (HDV, delta agent) is a defective RNA virus that uses the HBV surface antigen as a viral envelope. HDV can occur as a coinfection or superinfection in individuals infected with HBV, which may then progress to severe fulminant infection.[2]

Transmission of HDV can occur via infected blood or blood products and is primarily seen in intravenous drug users and hemophiliacs. HDV may also be transmitted through sexual activity. Serologic testing for HDV and anti-HDV is used to detect infection. Effective prevention of HBV will protect against HDV infection. The screening of the blood supply for HBV has altered the epidemiology of HDV. There is currently no treatment for HDV infection.[2]

Hepatitis E and G

Hepatitis E virus (HEV) is a nonenveloped, single-stranded RNA virus that is highly unstable due to the lack of a lipid membrane. Transmission, similar to HAV, is by the oral-fecal route. The primary method of spread is through contaminated drinking water[2] and occurs mostly in places with inadequate sanitary precautions.

Symptoms of disease commonly include malaise, nausea, abdominal pain, and/or fever. The infection is usually self-limiting, although there have been cases of fulminant hepatitis and chronic disease.[2] In pregnant patients infected with HEV, there is a higher risk of fulminant hepatitis. There is no HEV vaccine available, and treatment is palliative.

Hepatitis G virus (HGV) is caused by two isolated viruses that appear to be almost identical. They are single-stranded, positive-sense RNA viruses similar to HCV.[13] HGV is transmitted through blood and blood products, sexual activity, and perinatal contact. Due to similar transmission routes, HGV may be found in association with other hepatitis viruses, especially HCV. Individuals at risk are organ transplant and blood transfusion recipients, IV drug users, dialysis patients, and health care workers with exposure to blood and chronic HCV patients.[9] Diagnosis is based on detection of HGV RNA in serum one to four weeks after infection. Serum anti-HGV indicates past infection.[14] Although the rate of remission is low, little evidence exists that HGV causes significant liver damage, even with persistent viremia.[13]

Autoimmune hepatitis

Autoimmune hepatitis is a chronic inflammatory disease. Although the etiology is not clear, it is thought that environmental and viral factors may cause alterations in cellular markers on hepatocytes leading to an autoimmune response in genetically susceptible individuals.[15] The etiology appears to be related to antigen-specific and generalized suppressor defects that perpetuate the autoimmune response. The main finding in autoimmune hepatitis is IgG hypergammaglobulinemia, which may be due to chronic infections or alteration in immune response. Autoimmune hepatitis may lead to liver cirrhosis.[16]

Treatment protocols for autoimmune hepatitis patients usually include steroid therapy. If remission is not obtained by steroid therapy alone, azathioprine or its metabolite (6-mercaptopurine) may be added to the protocol.[15]

Fulminant hepatitis

Fulminant hepatitis is sudden, severe liver dysfunction which may lead to hepatocellular necrosis as well as hepatic encephalopathy.[17] Signs of fulminant hepatitis include jaundice, hepatomegaly, and right upper quadrant tenderness during the inflammatory stage. As necrosis occurs and progresses, the liver becomes atrophic and less readily palpable. With the onset of severe liver failure, liver enzymes, bilirubin, prothrombin time, and partial thromboplastin time will be elevated, while hemoglobin and hematocrit will decrease.[17] The prognosis for fulminant hepatitis is poor, and the treatment of choice is liver transplantation.[17]

HEMOCHROMATOSIS

Hereditary hemochromatosis is a disease in which there is a defect in iron metabolism resulting in malabsorption and iron deposits in the liver, pancreas, heart, kidneys, and other organs. The iron accumulation may lead to diabetes mellitus, cardiomyopathy, and cirrhosis. Mutations in the HFE gene have been proven to be the source of the defect in iron metabolism in 80% of patients.[18] Patients may also present with hepatomegaly and hyperpigmentation (especially in the face, neck, forearms, and legs). The severity is affected by genetic and environmental factors, such as iron intake, blood donation, and physiologic blood loss. Women tend to be affected at a later age than men.[19]

An association has been identified between hemochromatosis and hepatocellular carcinoma, especially in patients with both hemochromatosis and liver cirrhosis. In patients with hemochromatosis, the subsequent development of hepatocellular carcinoma is significantly associated with iron-free foci on biopsy.[20]

Once the diagnosis of hepatocellular carcinoma is made and the presence of the C282Y gene established, screening of siblings is indicated. Family members with C282Y homozygosity should be checked for serum transferrin saturation in addition to ferritin and liver enzyme levels. If transferrin saturation is greater than 45% and verified by a second fasting sample, further investigation is warranted.

Once the diagnosis of hemochromatosis has been made, patients should be prescribed a course of iron depletion therapy and monitoring. Therapeutic and maintenance phlebotomy may be performed with regular monitoring of hemoglobin, hematocrit, and serum ferritin levels.[20] Patients with hemochromotosis should avoid iron supplements and abstain from alcohol if liver abnormailities are present.

HEPATIC CIRRHOSIS

Hepatic fibrosis and its end stage, cirrhosis, are an increasing worldwide concern. Cirrhosis is the irreversible end result of fibrous scarring and normal hepatic architecture is replaced with interconnecting bands of fibrous tissue. Normal function is disturbed by the resulting inadequate blood flow and ongoing damage to hepatocytes. The most common etiologic factors resulting in cirrhosis are hepatitis B, hepatitis C, and excessive alcohol consumption. Other potential causative factors are immune-mediated damage, genetic abnormalities, and nonalcoholic steatohepatitis (NASH).[21] Liver fibrosis and cirrhosis are diseases marked by an increase in total liver collagen, as well as other matrix proteins that are disruptive to liver architecture and function.[22]

The major complications of cirrhosis are portal hypertension, hepatocellular carcinoma, and loss of function. Portal hypertension may result in variceal hemorrhage, ascites, and hepatic encephalopathy. Hemorrhage, most commonly from varices in the esophagus, is a severe complication of portal hypertension. Cirrhosis and hepatic encephalopathy may occur due to inadequate hepatic removal of nitrogenous compounds and other toxins.

The path to fibrosis and cirrhosis is mediated by hepatic stellate cells.[23] In the normal liver, stellate cells store retinoids and are present in the spaces of Disse. After injury, the stellate cells become myofibroblast-like and express contractile protein. The stellate cells proliferate and become the major source of the fibrillar collagens that characterize fibrosis and cirrhosis.[23] In areas of injury, cytokines are released by inflammatory cells and activate the stellate cells. Due to the role of inflammation in stellate cell activation, studies of interleukin-10 as a down-regulator of response and tumor necrosis factor alpha as a pro-inflammatory mediator may be valuable clinically for hepatitis C treatment.[24] Other areas of investigation involve the mediators of the fibrogenic reaction of stellate cells such as transforming growth factor beta one, a cytokine that is also involved in fibrosis of other organs, such as the lung and kidney. Signaling through soluble mediators such as transforming growth factor beta is key to the fibrogenic response. By modifying the secretion and/or activity of the aforementioned factors, fibrosis may be prevented.[22]

Current treatment for patients with cirrhosis includes removing the injury-causing stimulus, antiviral therapy, and liver transplantation.[22] For end-stage cirrhosis, transplantation is a highly successful treatment with a high survival rate. However, due to the increased demand, limited availability of organs, compatibility issues, as well as other factors, this option is not for all patients. Alternate treatments are being sought and studied, including antifibrotic therapy.[22]

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma is the most common primary cancer of the liver, the sixth most common cancer in men, and the eleventh most common cancer in women in the United States.[25] This cancer is a devastating disease with five-year survival rates around 2%.[26] The most common etiologic factors in hepatocellular carcinoma are HBV and HCV. In this condition, alpha fetoprotein levels may be elevated.[27] The incidence of hepatocellular carcinoma is rising, and this trend is expected to continue for years.[28]

The primary treatment for hepatocellular carcinoma is surgery if the tumor is respectable.[28] Unfortunately, many patients have unresectable cancers due to the proximity of the lesion to vital structures, metastases, or other co-morbidities.[29] Even after resection, a cirrhotic liver may regenerate poorly, posing a threat of liver failure and tumor recurrence.[28]

Postoperative therapies aimed at decreasing the rate of tumor recurrence and increasing survival rate are being studied.[28] Some drugs may hold promise, but consistent improvement in outcomes has not been confirmed.[30] If surgical resection is not possible due to underlying liver dysfunction, transplantation is an option.

Table I. Essential factors for appropriate dental management of patients with liver disease

- Comprehensive and current medical and dental histories
- Consultation with and/or referral to treating physician(s) prior to dental treatment
- Appropriate laboratory investigations
  - ○ Complete blood count with differential (erythrocyte count, leukocyte count, hemoglobin, hematocrit, platelet count)
  - ○ Prothrombin time
  - ○ Partial thromboplastin time
  - ○ International normalized ratio
  - ○ Bleeding time
  - ○ Liver function tests
  - ○ Others as needed
- Judicious use or avoidance of prophylactic and therapeutic dental medications that are metabolized in the liver and/or impair hemostasis
  - ○ Analgesics (acetaminophen, non-steroidal anti-inflammatory agents, opioids)
  - ○ Anesthetics
    - ■ Local (amides)
    - ■ General (halothane)
  - ○ Antibiotics (ampicillin, tetracycline)
  - ○ Antiplatelets (aspirin)
  - ○ Sedatives (long-acting benzodiazepines, barbiturates)
- Minimization of soft tissue trauma during dental procedures
- Consideration of hospital setting for advanced surgical procedures or severely coagulopathic patients

ORAL MANIFESTATIONS

The oral cavity may show evidence of liver dysfunction with the presence of hemorrhagic changes, petechiae, hematoma, jaundiced mucosal tissues, gingival bleeding, and/or icteric mucosal changes. HCV has been linked to the onset. Sjögren's syndrome[31] and chronic hepatitis have been associated with lichen planus in some studies.[32,33] Glossitis may be seen with alcoholic hepatitis, especially if combined with nutritional deficiencies. Ecchymosis and reduced healing after surgery may also be identified. In some cases, parotid gland enlargement is evident.[9] These oral changes often appear in combination with general signs and symptoms of liver disease such as fatigue, malaise, confusion, weight loss, nausea, vomiting, hepatomegaly, hemorrhagic changes, spider angiomas, edema, ascites, dark urine, and pale/clay-colored stool.

DENTAL MANAGEMENT

Disorders of the liver have many implications for a patient receiving dental treatment (Table I). Dental care providers should be aware of the potential for increased bleeding as well as drug toxicity. Thorough medical and dental histories are essential, including questions regarding hepatitis, jaundice, cancer, autoimmune disorders, HIV/AIDS, surgeries, family history, medications, alcohol intake, recreational drug use, sexual history, and bleeding tendencies.[27] It is prudent to discuss the details of the liver disease with a treating physician in order to provide the patient with a dental treatment plan that is safe and appropriate for the medical and dental conditions with which the patient presents.

Quite often, liver disease will result in depressed plasma levels of coagulation factors that need a careful evaluation of hemostasis prior to treatment. Patient testing should include CBC, PT, PTT, INR, bleeding time, and liver function tests. If any abnormal levels are discovered, consultation with a hematologist or hepatologist is suggested before beginning dental treatment. If oral surgical procedures are required, special attention should be paid to the minimization of trauma to the patient. As the risk of bleeding increases, an infusion of fresh frozen plasma may be indicated. Advanced oral surgical procedures or any dental procedures with the potential to cause bleeding performed on a patient with multiple or a severe single coagulopathy may need to be provided in a hospital setting.[7,34]

Certain sedatives (diazepam, barbiturates) and general anesthetics (halothane) impair detoxification in hepatic disease and should be used cautiously. Brain metabolism may be altered, and sensitivity to medications may increase. Encephalopathy can be triggered by sedatives and opioids.[27] Caution should be used in prescribing medications metabolized in the liver, such as methyldopa, isoniazid, nitrofurantoin, acetaminophen, nonsteroidal anti-inflammatory agents, phenytoin, phenobarbital, valproic acid, and some sulfonamides.[15]

Local anesthetics should be administered cautiously to patients with hepatic impairment. Most amides are primarily metabolized in the liver and therefore may reach toxic levels with lower doses of anesthetic. Articaine (plasma) and prilocaine (partly in lungs), however, have other sites of metabolism. Drug dosages and possible interactions should be discussed with a treating physician. In some cases, lower drug dosages are required, while some drugs (erythromycin, metronidazole, tetracyclines) should be avoided completely. Nonsteroidal anti-inflammatory agents should be used cautiously or avoided due to an increased risk of gastrointestinal bleeding and interference with fluid balance.[27] Prophylaxis with an antacid or histamine receptor antagonist may be considered to prevent gastritis and gastrointestinal bleeding associated with the hepatic dysfunction.[1] Any modifications in medication regimen should be made in conjunction with the suggestions of a treating physician.

REFERENCES

1. Little JW, Falace DA, Miller CS, Rhodus NL. Dental management of the medically compromised patient. 5th ed. St. Louis: Mosby; 1997.
2. Gillcrist JA. Hepatitis viruses A,B,C,D,E and G: implications for dental personnel. J Am Dent Assoc 1999;130:509-20.
3. Wolters LM, Niesters HG, de Man RA. Nucleoside analogues for chronic hepatitis B. Eur J Gastroenterol Hepatol 2001;13:1499-506.
4. Matthews GV, Nelson MR. The management of chronic hepatitis B infection. Int J STD AIDS 2001;12:353-7.
5. Dienstag JL, Isselbacher KJ. Acute viral hepatitis [Internet]. Columbus (OH): The McGraw-Hill Companies [cited 2004 Sep 12]. Available from: http://harrisons.accessmedicine.com.proxy.cc.uic.edu/server-java/Arknoid/amed/harrisons/co_chapters/ch295/ch295_p01.html.
6. Levy MJ, Herrera JL, DiPalma JA. Immune globulin and vaccine therapy to prevent hepatitis A infection. Am J Med 1998;105:416-23.
7. DePaola LG. Managing the care of patients infected with bloodborne diseases. J Am Dent Assoc 2003;134:350-8.
8. Larson AM, Carithers RL. Hepatitis C in clinical practice. J Intern Med 2001;249:111-20.
9. Wisnom C, Siegel MA. Advances in the diagnosis and management of human viral hepatitis. Dent Clin North Am 2003;47:431-47.
10. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Intern Med 2000;132:296-305.
11. Kelly D, Skidmore S. Hepatitis C-Z: latest treatment options. Arch Dis Child 2002;86:339-43.
12. Buratti S, Lavine JE. Drugs and the liver: advances in metabolism, toxicity, and therapeutics. Curr Opin Pediatr 2002;14:601-7.
13. Malnick SD, Lurie Y, Bass D. G(ee): A new hepatitis virus. J Clin Gastroenterol 1997;24:62-4.
14. Lodi G, Carrassi A, Scully C, Porter SR. Hepatitis G virus: relevance to oral health care. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88:568-72.
15. Al-Khalidi JA, Czaja AJ. Current concepts in the diagnosis, pathogenesis, and treatment of autoimmune hepatitis. Mayo Clin Proc 2001;76:1237-52.
16. Prandota J. Possible pathomechanism of autoimmune hepatitis. Am J Ther 2003;10:51-7.
17. D'Souza R, Foster GR. Diagnosis and treatment of chronic hepatitis B. J R Soc Med 2004;97:318-21.
18. Gochee PA, Powell LW. What's new in hemochromatosis. Curr Opin Hematol 2001;8:98-104.
19. Hash RB. Hereditary hemochromatosis. J Am Board Fam Pract 2001;14:266-73.
20. Niederau C, Strohmeyer G. Strategies for early diagnosis of haemochromatosis. Eur J Gastroenterol Hepatol 2002;14:217-21.
21. Zavaglia C, Airoldi A, Pinzello G. Antiviral therapy of HBV- and HCV-induced liver cirrhosis. J Clin Gastroenterol 2000;30:234-41.
22. Iredale JP. Cirrhosis: new research provides a basis for rational and targeted treatments. Br Med J 2003;327:143-7.
23. Sokol RJ. Liver cell injury and fibrosis. J Pediatr Gastroenterol Nutr 2002;35(Suppl 1):S7-10.
24. Jones DE. Autoantigens in primary biliary cirhosis. J Clin Pathol 2000;53:813-21.
25. Smukler AJ, Ratner L. Hepatitis viruses and hepatocellular carcinoma in HIV-infected patients. Curr Opin Oncol 2002;14:538-42.
26. Rilling WS, Drooz A. Multidisciplinary management of hepatocellular carcinoma. J Vasc Interv Radiol 2002;13(9 Suppl):S259-63.
27. Greenwood M, Meecham JG. General medicine and surgery for dental practitioners. Part 5: liver disease. Br Dent J 2003;195:71-3.
28. Johnson PJ. Hepatocellular carcinoma: is current therapy really altering outcome? Gut 2002;51:459-62.
29. Kruskal JB, Goldberg SN. Emerging therapies for hepatocellular carcinoma: opportunities for radiologists. J Vasc Interv Radiol 2002;13(9 Suppl):S253-8.
30. Bergsland EK, Venook AP. Hepatocellular carcinoma. Curr Opin Oncol 2000;12:357-61.
31. Haddad J, Deny P, Munz-Gotheil C, Ambrosini JC, Trinchet JC, et al. Lymphocyte sialadenitis of Sjogren's syndrome associated with chronic Hepatitis C virus liver disease. Lancet 1992;339:1425-6.
32. Carrozzo M, Grandolfo S, Carbonne M. Hepatitis C virus infection in Italian patients with oral lichen planus: A prospective case-control study. J Oral Pathol Med 1996;25:527-33.
33. Nagao Y, Sata M, Itoh K, Tawikawa K, Kameyama T. Detection of Hepatitis C. Virus RNA in Oral Lichen Planus and Oral Cancer Tissue. J Oral Pathol Med 2000;29:256-66.
34. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy. Part 1: coagulopathies from systemic disease. Br Dent J 2003;195:439-45.